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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
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Rec'd PCT/PTO 25 JAN 2005

PCT

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year) 13 MAY 2005

Applicant's or agent's file reference

GENO200.1.7/PCT

IMPORTANT NOTIFICATION

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US03/25027

08 August 2003 (08.08.2003)

08 August 2002 (08.08.2002)

Applicant

EVOLUTIONARY GENOMICS, LLC

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Mail Stop PCT, Attn: IPEA/US

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Form PCT/IPEA/416 (July 1992)

Authorized officer

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | | |
|--|---|--|--|
| Applicant's or agent's file reference GENO200.1.7/PCT | | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US03/25027 | International filing date (day/month/year) 08 August 2003 (08.08.2003) | Priority date (day/month/year) 08 August 2002 (08.08.2002) | |
| International Patent Classification (IPC) or national classification and IPC IPC(7): G06F 17/00, 17/10, 17/11; C12Q 1/68, 1/02; G01N 33/00, 33/15 and US Cl.: 702/19, 20; 435/6, 29; 800/3; 436/183 | | | |
| Applicant EVOLUTIONARY GENOMICS, LLC | | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|--|--|
| Date of submission of the demand 08 September 2004 (08.09.2004) | Date of completion of this report 15 April 2005 (15.04.2005) |
| Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/ US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230 | Authorized officer James Martinell <i>James Martinell</i> Telephone No. (703) 308-0196 |

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US03/25027

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed.

☒ the description:

pages 1-41 as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____

☒ the claims:

pages 42 and 43 as originally filed

pages NONE, as amended (together with any statement) under Article 19

pages NONE, filed with the demand

pages 44 and 45, filed with the letter of 05 March 2004 (05.03.2004)

☐ the drawings:

pages NONE, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____

☐ the sequence listing part of the description:

pages NONE, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item. These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☒ the claims, Nos. 14

☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/25027

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)

Claims 5-8 and 10-13 YES

Claims 1-4 and 9 NO

Inventive Step (IS)

Claims 5-8 and 10-13 YES

Claims 1-4 and 9 NO

Industrial Applicability (IA)

Claims 1-13 YES

Claims NONE NO

2. CITATIONS AND EXPLANATIONS

Claims 1-4 and 9 lack novelty under PCT Article 33(2) as being anticipated by either one of Messier et al (U.S. Patent No. 6,274,319) or Eyre-Walker et al (Proc. Natl. Acad. Sci. USA. 95: 4441 (1998)). Messier et al teaches a method of sequence comparison for identification of a bottleneck (e.g., see column 21, line 10 through column 24, line 12) which is embraced by the claims. Likewise, Eyre-Walker et al teaches a method of sequence comparison for identification of a bottleneck (e.g., see pages 4441-4443) which is embraced by the claims.

Claims 5-8 and 10-13 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed methods.

Claims 1-13 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

----- NEW CITATIONS -----

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comprising:

a) aligning homologous nucleotide sequences of at least about two at least two individual organisms, wherein said at least two individual organisms are selected from the group consisting of individual organisms of a single strain, individual organisms of different strains, individual organisms of the same species, individual organisms of different species, and any combination of the foregoing; and

b) detecting a region of polynucleotide sequence for which the number of nucleotide differences/site indicates an evolutionary bottleneck;

c) determining that the region identified in b) is a non-coding region, whereby a regulatory element is identified.

6. The method according to any one of claims 1-4, wherein the identifying the number of nucleotide differences/site is calculated by $\pi = 1/[n(n-1)/2] \sum_{i < j} \Pi_{ij} / L$, n is number of sequences, where i and j represent any two sequences being compared in a series of sequences and L = sequence length.

7. The method according to any one of claims 1-4, further comprising determining if the region displays a signature of positive selection.

8. The method of Claim 9, wherein said determining comprises calculating a Ka/Ks value.

10. The method according to any one of claims 1-4, wherein the method is performed in an automated pipeline.

11. The method according to any one of claims 1-4, wherein the at least two strains and/or individuals of a single strain is at least ten strains and/or individuals of a single strain.

12. The method of Claim 11, wherein the at least two strains and/or individuals of a single strain is at least fifteen strains and/or individuals of a single strain.

13. A method for identifying an agent which may modulate a commercially or aesthetically relevant trait that is unique, enhanced or altered in the domesticated organism as

compared to other domesticated or ancestral species of the domesticated organism, said method comprising contacting at least one candidate agent with a cell, model system or transgenic plant or animal that expresses a polynucleotide sequence that is an evolutionary bottleneck, wherein the agent is identified by its ability to modulate function of the polypeptide encoded by the polynucleotide.

14. A method for correlating a nucleotide sequence which is an evolutionary bottleneck to a commercially or aesthetically relevant trait that is unique, enhanced or altered in a domesticated organism, comprising:

- a) identifying a nucleotide sequence which is an evolutionary bottleneck; and
- b) analyzing the functional effect of the presence or absence of the identified sequence in the domesticated organism or in a model system.